

## HORMONES OF THE ADRENAL GLAND\*

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The adrenals were first described by Eustachius in 1563 but it was not until 1855 that Addison, an English physician, published a clue as to their function. He was able to associate a certain group of symptoms with disease of these glands. Fatigue, pigmentation and digestive disturbances were most prominent. His observations focused attention on the vital nature of these organs. Very soon it was proven by experiments on animals that the adrenals are necessary for life. The next important contribution came in 1894 when Oliver and Schafer demonstrated that an extract of the adrenal produced a marked rise in blood pressure. This was due to a substance obtained from the central part or medulla of the gland. Abel isolated the benzoyl compound of this substance and then Takamine and Aldrich, working independently, isolated the active principle by a method which was commercially feasible. Abel introduced the name epinephrin and Takamine that of adrenalin for this new compound. Its synthesis was accomplished by Stoltz in 1904.

### SECRETION OF EPINEPHRIN

One can determine the amount of epinephrin in the adrenals by removing and extracting them, but that gives no information as to the amount normally secreted into the blood stream. This can be determined, however, by collecting the blood as it pours from the gland, and then assaying this blood for its epinephrin content. By cutting the sensory nerves of the region concerned in preparing the adrenal vein for cannulation, it is possible at a later date to carry out this procedure without the use of anesthesia. Inhibition of a contracting piece of intestine is used in the assay of the epinephrin. Satake, Watanabe and Sugawara found that during serene existence 0.00003–0.0001 mg. is secreted per min. per kg. This would amount to 0.4–1.4 mg. per day in a 10 kg. dog. If man secreted a proportionate amount the value attained would be 3–10 mg.

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in a day. However, without actual determination we do not know whether such an assumption is justified. Some investigators have obtained higher values than those given by Satake et al. Differences in the method employed as well as the conditions of the experiment may explain the discrepancy. It is difficult to prove that this amount of epinephrin has a physiological effect when secreted in the general circulation over a period of twenty-four hours, although if released at one time the effect would be lethal.

Serenity is often interrupted by stimuli which will increase the output of epinephrin. Exercise as moderate as walking produces an appreciable effect. Cold by its stimulation of sense organs may cause a decided increase. Emotional excitement may have a marked influence. Exposure to heat intense enough to cause a decided rise in body temperature may lead to a seven-fold increase in the output. Hemorrhage in which as much as one-third of the blood volume is lost causes a five-fold increase. Blood pressure maintained at shock level (40 mm. Hg) for one hour or longer will set free a thirty-fold increase. Marked reduction in blood sugar also increases the epinephrin output. Thus insulin evokes an outpouring of epinephrin which in turn raises the blood sugar. This explains the greater sensitiveness to insulin when the adrenal medullae are destroyed. These merely serve as examples of the wide variety of influences which affect the output of epinephrin.

#### EFFECT OF EPINEPHRIN

The amount of epinephrin secreted under physiological stimulation is enough to produce demonstrable physiological effect. One notes first the change in circulation. The heart is stimulated; blood vessels in the skin, in the mucous membranes and some abdominal organs are constricted, while those in skeletal muscle are dilated. In spite of these effects there is no evidence that epinephrin plays a part in the maintenance of normal blood pressure. Under the influence of epinephrin the spleen forces more red cells into active circulation. Blood coagulation is accelerated. The bronchioles are dilated permitting freer exchange of air with the lungs. Reduction in blood flow and inhibition of movement in the alimentary canal retard digestion. Epinephrin mobilizes the carbohydrates in the body as shown in the diagram (Fig. 1). Blood sugar is increased at the expense of liver glycogen stores while muscle

glycogen is transformed into lactic acid which is later carried to the liver and transformed into glycogen. At the same time the utilization of carbohydrates is increased. When the concentration of epinephrin becomes sufficient general metabolism is increased.

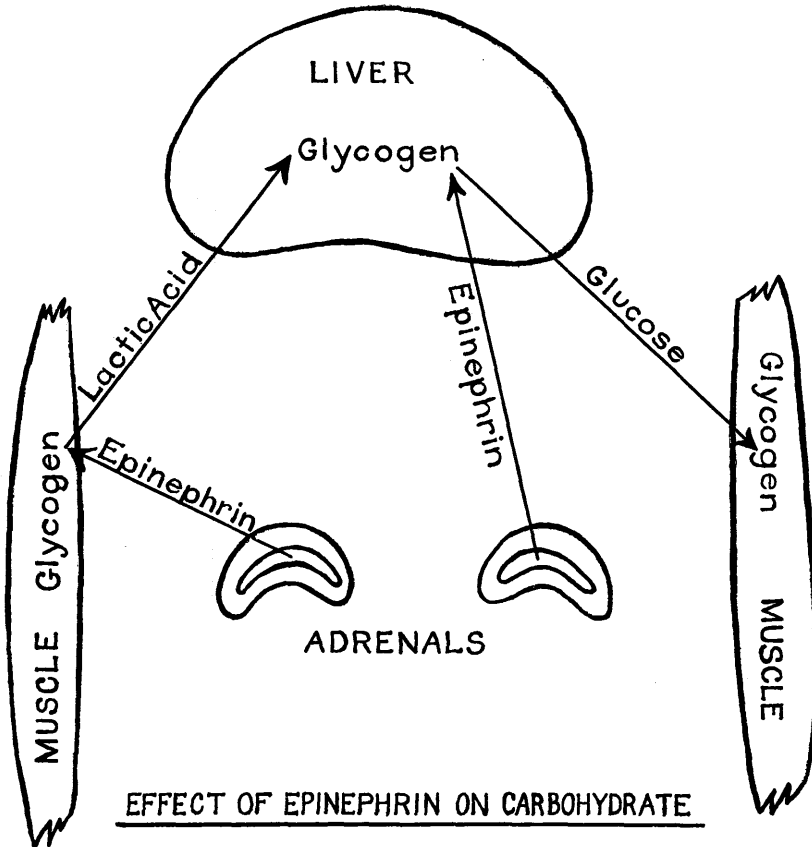


Fig. 1. Effect of epinephrin on carbohydrate.

A careful survey shows us that epinephrin acts on those tissues supplied by the sympathetic nervous system and in the same manner that this system does, stimulating where the latter stimulates and inhibiting where the latter inhibits.

Epinephrin action is fleeting. Any continued effect through its influence, therefore, must be sustained through continued secretion. Thyroxin increases the sensitiveness to epinephrin while thyroidectomy decreases the response as much as fifty per cent.

The total amount of epinephrin in both adrenals of a man is about 10 mg. This much or more may be secreted in 24 hours. Therefore there must be constant renewal. From experiments on animals it has been shown that it is difficult to exhaust the supply. Certain poisons like diphtheria toxin do this most effectively. Severe infections, starvation, convulsive doses of insulin and exophthalmic goiter also cause marked depletion (Corbett).

#### FUNCTION OF THE MEDULLA

The medulla through its secretion of epinephrin reinforces the action of the sympathetic nervous system. In times of stress its influence is most marked. This led Cannon to propose the emergency theory of the medulla. In the reactions of combat, flight or major emotions epinephrin helps to mobilize the resources of the organism for the emergency. However, epinephrin may influence the organism to a lesser degree in less strenuous states.

#### TUMOR OF MEDULLA

Occasionally a tumor may develop in the medulla. The symptoms are hypertension, headache, palpitation, perspiration, vomiting, tremor and rapid breathing which most often occur at intervals. The attacks may last a few minutes or longer and the blood pressure rise to 180 mm. Hg or more. Death may occur from pulmonary edema. The release of excessive amounts of epinephrin account for the symptoms produced. Removal of the tumor leads to disappearance of the symptoms. Such tumors have been found to contain much larger amounts of epinephrin than that found in a normal gland.

#### ADRENAL CORTEX

It has been known for eighty years that the adrenal is vital to the organism, but not until 1917 (Wheeler and Vincent) was it shown that only the outer part, the cortex, is essential to life.

No direct proof of a vital hormone of the cortex was published until 1927, when two groups of investigators, one in Cleveland (Rogoff and Stewart) and the other at Buffalo (Hartman, MacArthur and Hartman) demonstrated that an extract of the adrenal cortex could prolong the lives of completely adrenalectomized animals. The extract prepared by

the second group was free from epinephrin. The hormone essential to life was named interrenalin by the Cleveland group and cortin by the Buffalo group. Beginning in 1930 improvements in the method of preparation were described by Swingle and Pfiffner and by Hartman and Brownell (1). Not only is it possible to maintain the lives of adrenalectomized animals indefinitely with such extracts, but they frequently can be revived from collapse. The first severe case of Addison's



Fig. 2. Shows pigmentation of Addison's disease in contrast to a normal subject. Note the general bronzing with black freckles especially on the face.

disease kept alive by cortin was described by Hartman, Aaron and Culp. He was revived from a comatose condition and survived until he contracted pneumonia nearly eight months later.

In spite of numerous reports to the contrary, cortin has not yet been isolated. The most recent report of DeFremery, Laqueur, Reichstein, Spanhoff and Ulydert claims a highly active crystalline cortical hormone which melts at  $180^{\circ}$ – $182^{\circ}$ . Their animal test is not entirely convincing because they used 0.6–2.5 mg. of their substance with added salt in dogs weighing 11–18 kg. Without added salt ten times as much was required.

Swingle and Pfiffner's non-crystalline preparation requires 0.03–0.045 mg. for dogs of corresponding size without added salt. Our best preparation which is amorphous would require 0.011–0.03 mg. for dogs of corresponding size.

All evidence for the existence of cortical hormones depends upon biological tests. So far the only critical test for the vital hormone is the ability to maintain the normal activities of completely adrenalectomized animals. There may be other hormones not yet recognized. This possibility makes it desirable to analyze the responses of normal animals as well as adrenalectomized animals to different preparations from the adrenal cortex.

#### INFLUENCE ON PIGMENTATION

Although pigmentation never occurs in the adrenal insufficiency of animals it is often present in man (Fig. 2). It may begin at any time in the course of development of Addison's disease or it may be absent altogether. In color it ranges from tan to negroid; occasionally it is gray or olive. The intensity is greatest in regions exposed to light or pressure. Its distribution varies from a uniform shading over large areas to blotches or freckles. It may extend to the mucous membranes. The symptoms of the disease bear no direct relation to the intensity of the pigmentation. Treatment with cortical extract may cause a slow disappearance of pigmentation. Whether pigmentation is due to cortin insufficiency or to the absence of some other substance probably can not be determined until pure hormone is available.

#### RELATION OF CORTIN TO ELECTROLYTE AND FLUID SHIFT

One of the first signs of adrenal insufficiency is loss of desire for food and water and reduction in absorption from the alimentary canal. This lowers the intake of water and salts. In normal individuals adjustments are made for such reductions without difficulty, the salt and water of the body being conserved through decreased excretion by the kidney. In cortical insufficiency the kidney allows sodium chloride to escape in larger amounts than usual (Fig. 3) so that the body reserve is seriously depleted. The volume of the blood plasma becomes reduced due to loss of water through the kidneys, although at first some of this water escapes into the tissues. Later the tissues also become depleted (Fig. 4). The ability of cortin

to restore the plasma volume without administration of water and salt indicates that the changes are not limited to the kidney. Cortin must bring about a readjustment in the distribution of the electrolytes and fluid within the body itself.

## ADDISON'S DISEASE

### EXCRETION OF ELECTROLYTES

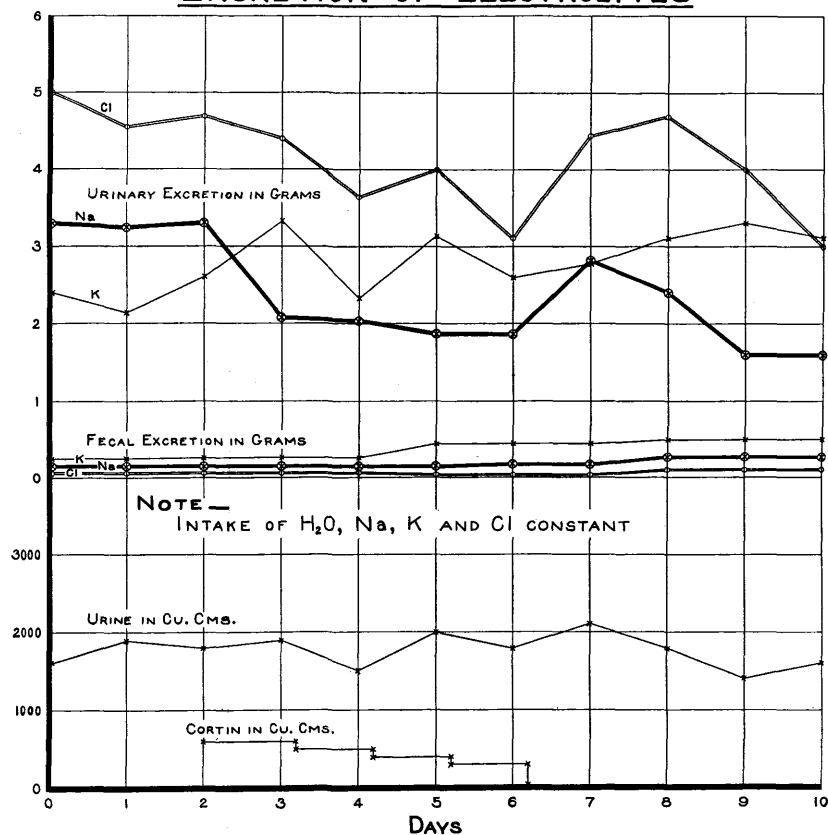


Fig. 3. Renal excretion of electrolytes in a case of Addison's disease. Note that Na and Cl excretion is reduced while the K excretion is increased after cortin injections.

At times it is possible to effect restoration in a subject who is in collapse. However, complete restoration usually requires the administration of water and salt, as well as cortin. Any demand which increases the need for fluid shift is poorly met in

cortical insufficiency. Hemorrhage which may be insignificant in the normal subject may produce collapse in insufficiency. Resistance to heat is much diminished. Water fails to shift as readily from the reservoirs such as skin and liver, resulting in less available water for evaporation and heat loss. Cortical insufficient subjects develop serious symptoms and succumb more readily to heat than do normals (Hartman, Brownell and Lockwood).

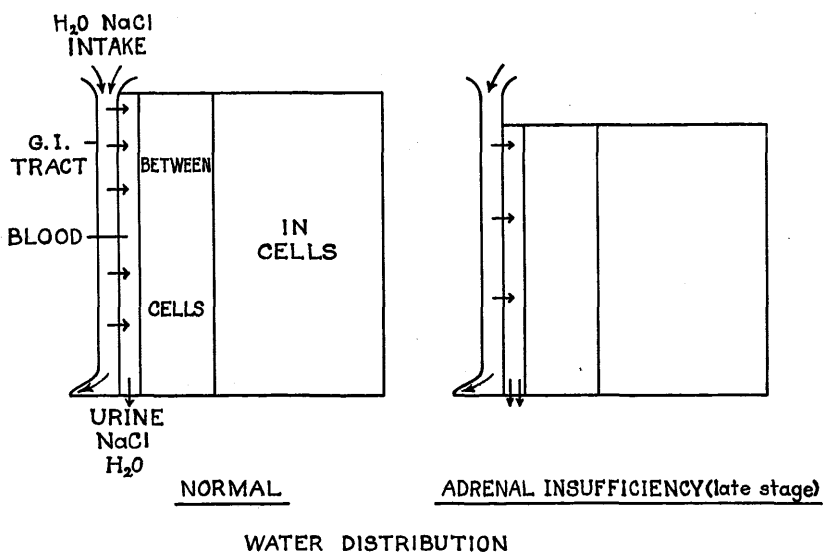


Fig. 4. Distribution of water in well established adrenal insufficiency compared with the normal.

Increase in the NaCl intake may ameliorate the symptoms of early cortical insufficiency but it is unavailing in the late stage. Cortin not only enables the kidney to maintain the threshold for electrolyte excretion which exists under normal conditions, but when injected into normal individuals in large amounts raises the threshold above normal for NaCl but lowers that for potassium. These effects persist for several hours following a single injection.

Sodium chloride depletion in itself may cause the development of symptoms (McCance). These are weakness, lassitude, cramps and severe cardio-respiratory distress on exertion.



## RELATION TO THE NERVOUS SYSTEM

In adrenal insufficiency whether experimental or pathological (Addison's disease), symptoms develop which indicate marked changes in the nervous function. Not only does fatigue come on more easily but there is disinclination to muscular or mental effort. Loss in interest in surroundings may lead to a state of inertia which verges on coma. On the other hand the subject may be easily irritated and may even become disoriented. The cerebral manifestations especially in the late stage of Addison's disease may be treated by the psychiatrist without recognition of the disease. The insomnia, exhaustion, incompetence and confusion are no different than may appear in conditions not involving the adrenal. The administration of cortical extract corrects these conditions when due to cortical insufficiency. The effect might be the result of action on some primary function which indirectly influenced the nervous system such as the distribution of electrolytes or it might be due to direct action on the nervous system itself. However, observations of Hartman and Lockwood seem to show that cortin affects the reflexes directly because they become more readily fatigued in adrenalectomized rats without cortin than in similarly operated animals with cortin. This hormone influences the nervous system in conditions without obvious adrenal insufficiency. In some cases in which there is organic neurological change cortin improves the motor functions and the mental status. Fatigue is diminished with a concomitant increase in strength. Myotonic manifestations and fibrillation, when present, are decreased. A sense of well-being replaces depression and irritability disappears. (Hartman, Beck and Thorn.) Normal individuals at times respond, the immediate effect being drowsiness and release of nervous tension. These effects are not due to suggestion because sheep in a state of neurosis due to overtaking the nervous system in conditioned reflex experiments, show marked improvement under cortin therapy. (Liddell, Anderson, Kotyuka and Hartman.) This neurosis is characterized by extreme excitement, uncooperative behavior and spontaneous nervous twitching movements of the limb concerned in the reaction. Administration of cortical extract increased the vigor of the conditioned reflex and decreased the frequency of the nervous movements. The improvement persisted for more than three weeks after the

last injection. Increased resistance to fatigue, which persisted longer than 47 days after cortical extract injections were discontinued, had previously been observed in a patient with muscular dystrophy (Hartman and Thorn). The assumption is made that cortin is responsible for these effects.

#### EFFECT ON METABOLISM

Metabolism is lowered as much as 25 per cent in cortical insufficiency. In other words the sum of the chemical changes in the body is reduced that much under basal conditions. When there is stress the difference is augmented. Upon exposure to cold adrenalectomized animals may produce the extra heat required for a short time but this finally fails so that the temperature drops. Reflex activity is involved in the reaction to cold. It is possible that eventually the failure of the body musculature to produce more heat is due in part to fatigue of these reflexes as well as to depleted carbohydrate reserves. In adrenalectomized animals not exposed to cold there is a reduction in carbohydrate stores. This is not entirely accounted for by the lowered food intake because a twenty-four hour fast causes almost complete disappearance of liver glycogen in operated animals but not in normal animals. The blood sugar of the operated animals is also lowered. Muscle glycogen eventually falls. Adrenalectomized dogs whose electrolytes are maintained with cortin or without cortin by the administration of large amounts of sodium salts show a decided fall in blood sugar (Harrop et al.). This suggests that there may be another hormone which is concerned with carbohydrate metabolism. Such a view is supported by Long, who found that cortin did not maintain diabetes undiminished in adrenalectomized-depancreatized cats. We (Hartman and Brownell (2)) have been able to maintain the high blood sugar and sugar excretion in the urine in similar fed animals by large amounts of cortin provided the animals had not lost too much weight. In a fed dog with both adrenals and pancreas removed it has also been possible to maintain the high sugar values with cortin but the ketosis was much diminished (unpublished work of K. A. Brownell). The enlargement of the cortex produced by injections of insulin (Riddle) also gives evidence of a relation of the cortex to carbohydrate metabolism.

Cortical extract has an effect on respiratory metabolism in normal individuals according to observations of Hitchcock

and Grubbs in our laboratory. It reduces the oxygen consumption under conditions requiring more oxygen as in moderate exercise. The average reduction in eleven subjects was nearly 6 per cent during standing and about 14 per cent during walking. This seems to indicate an increase in muscular efficiency. The effect persists for several days after the extract is discontinued. This persistence reminds one of the after effect in neurotic sheep and in occasional patients. (See nervous system.)

#### VITAMINS

It has been known for a long time that the adrenal cortex hypertrophies in vitamin B<sub>1</sub> and C deficiencies. Another suggestion of a relation between the cortex and vitamin C is the observation that in late stages of adrenal insufficiency hemorrhages may occur from the gums and in the alimentary canal, a condition similar to that found in scurvy. We (Lockwood and Hartman) have studied the effect of cortical extracts in deficiencies of these vitamins. In the preparation of extract ethyl ether was employed at one stage to avoid inclusion of vitamins B<sub>1</sub> and C which are found in the cortex. These vitamins are insoluble in ether (Sherman and Smith). Additional evidence of the absence of vitamin C was obtained by the spectrographic method (Lockwood, Swan and Hartman).

Injection of cortical extract delayed the weight loss and postponed the onset of signs and symptoms in both avitaminosis B<sub>1</sub> and C. In order, as we thought, to reduce the active adrenal tissue we removed one adrenal in some animals. The results were just the reverse of what was expected. On both the B<sub>1</sub> and C free diets such an operation produced an effect similar to the injection of cortical extract. However, this did not occur if we waited about three weeks after the adrenalectomy before starting the vitamin free diet. It seemed that there was an overproduction of this ameliorating substance in the remaining adrenal for about three weeks after the operation.

Extract is most effective early in the avitaminosis when some vitamin from the pre-experimental period is still available in the organism. It is also more effective when a partial protective amount of the vitamin is fed. These observations suggest that cortical extract aids in the utilization of vitamins B<sub>1</sub> and C. Our extract contained significant amounts of cortin as judged by tests on adrenalectomized animals. Cortin or some unknown substance in the extract must have been responsible for the effects in vitamin deficiencies.

## CORTILACTIN

Adequate amounts of cortical extract enable adrenalectomized animals to give birth to young. Some time ago we (Brownell, Lockwood and Hartman) reported that cortical extract could be divided into two fractions, one containing cortin and the other a substance (cortilactin) necessary for lactation. It was possible to make this separation only under certain conditions. Cortex was extracted with 90 per cent alcohol. After removing the alcohol by vacuum distillation from the resulting extract the residue was taken up with ethyl ether. Ether was removed in vacuo from the ether extract. The residue was extracted with 70 per cent alcohol. The resulting solution was chilled to  $-12^{\circ}$  C. The lipids which were precipitated contained the factor necessary for lactation. Cortin remained in solution. Ordinary methods of preparing cortical extract do not separate the lactation factor from cortin. Cortin alone does not seem to enable adrenalectomized rats to lactate sufficiently. If cortilactin is added or if it has not been separated from cortin in the preparation of the extract, lactation is well supported. A positive effect on milk secretion has been obtained in the human being with cortilactin (unpublished work of Thorn and Hartman). Eight patients carefully controlled in the hospital have been studied. All were secreting very inadequate amounts of milk. Six of these showed increased milk production within 48 hours after starting the injections. The remaining two developed the typical sensation of tingling in the breast but no milk secretion. In one of the patients who responded with increased milk secretion, the amount of milk secreted fell to zero after cortilactin was discontinued.

## CORTIPRESSIN

Although the blood pressure of adrenalectomized animals is maintained by cortin, in some cases of Addison's disease seemingly adequate cortin treatment often does not re-establish the normal blood pressure level. Therefore it is possible that an additional factor is lacking. Looney and Darnell have found that a glycerol extract of the adrenal cortex administered by mouth in the human-being causes a prolonged increase in blood pressure. The marked rise occurs after four or five days and disappears in ten to fourteen days after withdrawal. The active substance is insoluble in fat solvents and is more

stable toward alkali than is cortin. They have named the substance cortipressin. We have employed a glycerol extract of the cortex in the treatment of Addison's disease but the effect on blood pressure is not striking.

#### ADRENOSTERON

Reichstein has isolated a compound which has about one-fifth the potency of the male sex hormone, androsteron. He calls the new compound adrenosteron. Frequently tumors of the adrenal cortex are found in cases of abnormal masculine development. Young boys so affected are precocious in both growth and sexual development. Females so affected change to the masculine type. The distribution of the hair and the character of the voice change, while menstruation ceases if it has begun. Removal of the tumor is followed by reversion to normal. Excessive production of adrenosteron might explain the changes resulting from cortical tumors.

#### CONTROL OF THE ADRENAL

Although the adrenal is well supplied with nerve fibers, their influence seems to be confined to the medulla. How is the cortex controlled? Within six days after hypophysectomy the adrenals of the rat are reduced to one-half the weight of the controls; maximum atrophy is reached in thirty days. This is largely due to changes in the cortex. All zones show marked reduction in the cytoplasm (Smith). The atrophied cortex still produces the vital hormone for if removed the animal dies of adrenal insufficiency. However, its production is probably inadequate because symptoms of cortical insufficiency develop from hypophysectomy. In hypophysectomized rats removal of one adrenal does not lead to hypertrophy of the remaining gland as it does in normal animals (Reiss, Balint and Aronson). Pituitary preparations restore degenerating adrenal cortex or, in normal animals, can increase the size of the cortex as much as two-fold (Emery and Atwell). Thus it has been demonstrated that the pituitary plays a major role in cortical control through its production of the adrenotropic hormone.

#### RESPONSE OF THE CORTEX TO STRESS

It is well known that in adrenal insufficiency there is greater susceptibility to infections, toxins, cold, heat, exercise and trauma. In order that these conditions be met considerably

more cortin is required. Cortin, therefore, has an emergency function as well as a sustaining function. Various stresses if repeated with sufficient frequency can increase the weight of the adrenals. Examples are shown in Fig. 5 in which the relative adrenal weights of the adrenals of rats under stress are

## RESPONSE OF ADRENAL TO STRESS

### TRAUMA

PIECE OF MUSCLE REMOVED TWICE A WK. FOR 5 WKS

545%

### COLD

20 TO 75 HRS DURING 3 TO 14 DAYS

10.9%

### EXERCISE

TWO HOURS DAILY FOR 12 DAYS

14.29%

### TOXIN

5 TO 25 BILLION STAPHYLOCOCCUS AUREUS  
DAILY FOR 30 DAYS

ADRENAL WEIGHT PER CENT GAIN OVER CONTROLS ————— 22.9%

Fig. 5. Response of adrenal to stress (rat), gain shown in black.

compared with control litter mates. The cortex is largely responsible for the increase in weight.

Although a part of the adrenal tissue is adequate to maintain the organism under quiet conditions, stress requires the functioning of all of the adrenal tissue. Rats with one adrenal removed are unable to produce as much heat when exposed to cold as when both adrenals are intact. For this reason they do not withstand cold so well (Horvath), Fig. 6.

COMPENSATORY HYPERTROPHY

If adrenal tissue is destroyed by disease or other cause, does the remaining tissue have the power to regenerate and if so can it replace the amount of tissue lost? The need for reserve adrenal tissue in stress makes this a very important question.

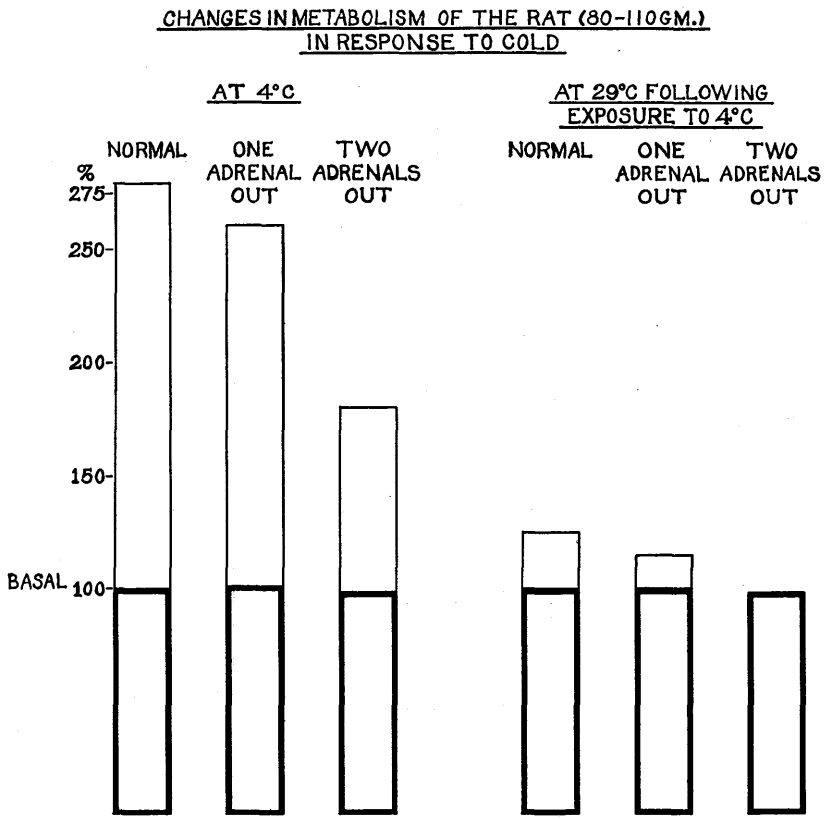


Fig. 6. Changes in metabolism of the rat in response to cold.

The failure to find evidence of regeneration of adrenal tissue at autopsy in Addison's disease may be explained by the assumption that had there been regeneration the patient would not have come to autopsy. It seems necessary to use animals to test the possibility of hypertrophy.

In young rats removal of one adrenal results in the hypertrophy of the remaining gland on the average of sixty per cent. (MacKay and MacKay.) This is far short of compensation.

Destruction of part of the adrenal tissue by cautery in cats is not followed by significant hypertrophy (Hartman). It is possible that the development of scar tissue from cautery prevented regeneration. Therefore, experiments were per-

TABLE I

SEX	TIME (DAYS) ELAPSED AFTER		BODY WEIGHT		WEIGHT OF ADRENAL	
	First Operation	Second Operation	Original gm.	At End gm.	Right gm.	Left gm.
F	126	64	2050	1340 (died)		0.055 0.044 <hr/> 0.099
M	401	281	3675	4260	0.175	0.112 0.125 <hr/> 0.237
F	329	268	1800	2380	0.121	0.055 0.089 <hr/> 0.144
F	333	216	1475	2225	0.114	0.063 0.038 <hr/> 0.101
M	354	294	1995	3100	0.149	0.067 0.104 <hr/> 0.171
F	399	282	2650	3150	0.245	0.168 0.119 <hr/> 0.287
M	399	281	3300	3880	0.160	0.086 0.075 <hr/> 0.161

formed in which part of the left adrenal was removed by a sharp scalpel. The piece removed was measured and weighed. Months later the right adrenal was removed, measured and weighed. From two to nine months after removal of the right adrenal the remainder of the left adrenal was removed, measured



and weighed, the accompanying table (Table I) presents the results. The weights of the first and second pieces of the left adrenal were added together. A comparison of this sum with the weight of the right adrenal shows that there could not have been a great amount of regeneration if one assumes that the right and left glands are not greatly different in size. The piece remaining *in situ* never regenerates enough to compensate in size for the tissue removed. When accessory adrenals are present in those animals which survive for a considerable time following adrenalectomy, the accessories do not become very large. In four cats the largest which we have observed (300 days after complete adrenalectomy) has been 55 mg. We are forced to conclude that although a small amount of regeneration of adrenal tissue takes place, there is never complete compensation.

TABLE II

HORMONES	FUNCTION
Epinephrin.....	Reinforces sympathetic nervous system.
Cortin.....	Maintains electrolyte balance. Required by nervous system. Aids in utilization of Vitamins B <sub>1</sub> and C. Necessary in metabolism of carbohydrate and fat.
Cortilactin.....	Required for lactation under certain conditions.
Cortipressin.....	Raises blood pressure.
Adrenosteron.....	As male sex hormone

## CONCLUSION

Two hormones of the adrenal are definitely established. One, epinephrin, is the only hormone indicated from the medulla. The other, cortin, is but one of a number indicated from the cortex (Table II). The function of cortin is somewhat indefinite. It maintains electrolyte balance and seems to be required by the nervous system. It may be the factor which aids in the utilization of vitamins B<sub>1</sub> and C. Some other factor in addition to cortin seems to be necessary for the metabolism of carbohydrate and fat. Other provisional hormones are cortilactin, cortipressin and adrenosteron. Further purification of the factors in the cortex will be required to establish some of them as hormones.

## BIBLIOGRAPHY

- Abel, J. J. Method of preparing epinephrine and its compounds. *Bull. Johns Hopkins Hosp.*, Vol. 13, p. 29, 1902.
- Addison, T. On the constitutional and local effects of disease of the suprarenal capsules. Lond., 1855, S. Highley.
- Aldrich, T. B. A preliminary report on the active principle of the suprarenal gland. *Am. J. Physiol.*, Vol. 5, p. 457, 1901.
- Brownell, K. A., J. E. Lockwood and F. A. Hartman. A lactation hormone of the adrenal cortex. *Proc. Soc. Exper. Biol. and Med.*, Vol. 30, p. 783, 1933.
- Cannon, W. B. The emergency function of the adrenal medulla in pain and the major emotions. *Am. J. Physiol.*, Vol. 33, p. 356, 1914.
- Corbett, J. F. Suprarenal gland in anesthesia. *J. A. M. A.*, Vol. 79, p. 543, 1922.
- DeFremery, P., E. Laqueur, T. Reichstein, R. W. Spanhoff and I. E. Ulydert. Corticosteron, a crystallized compound with the biological activity of the adrenal-cortical hormone. *Nature*, Vol. 139, p. 26, 1937.
- Emery, F. E. and W. J. Atwell. Hypertrophy of the adrenal glands following administration of pituitary extract. *Anat. Rec.*, Vol. 58, No. 1, Dec., 1933.
- Harrop, G. A., L. J. Soffer, W. M. Nicholson and M. Strauss. Studies on the suprarenal cortex—the effect of sodium salts in sustaining the suprarenalectomized dog. *J. Exp. Med.*, Vol. 61, p. 839, 1935.
- Hartman, F. A. Chronic adrenal insufficiency produced by cautery. *Endocrin.*, Vol. 17, p. 46, 1933.
- Hartman, F. A., A. H. Aaron and J. E. Culp. Use of cortin in Addison's disease. *Endocrin.*, Vol. 14, p. 438, 1930.
- Hartman, F. A., G. M. Beck and G. W. Thorn. Improvement in nervous and mental states under cortin therapy. *J. Nerv. and Ment. Dis.*, Vol. 77, p. 1, 1933.
- <sup>1</sup>Hartman, F. A., and K. A. Brownell. The hormone of the adrenal cortex. *Proc. Soc. Exper. Biol. and Med.*, Vol. 27, p. 938, 1930.
- <sup>2</sup>Hartman, F. A., and K. A. Brownell. Relation of adrenals to diabetes. *Proc. Soc. Exper. Biol. and Med.*, Vol. 31, p. 834, 1934.
- Hartman, F. A., K. A. Brownell and J. E. Lockwood. Studies indicating the function of cortin. *Endocrin.*, Vol. 16, p. 525, 1932.
- Hartman, F. A., and J. E. Lockwood. Effect of cortin on the nervous system in adrenal insufficiency. *Proc. Soc. Exper. Biol. and Med.*, Vol. 29, p. 141, 1931.
- Hartman, F. A., C. G. MacArthur and W. E. Hartman. A substance which prolongs the life of adrenalectomized cats. *Proc. Soc. Exper. Biol. and Med.*, Vol. 25, p. 69, 1927.
- Hartman, F. A., and G. W. Thorn. The effect of cortin in asthenia. *Proc. Soc. Exper. Biol. and Med.*, Vol. 29, p. 49, 1931.
- Horvath, S. M. The effect of adrenalectomy on the metabolic response of the albino rat to cold. *Proc. Am. Physiol. Soc.*, 1937.
- Liddell, H. S., O. D. Anderson, E. Kotyuka and F. A. Hartman. Effect of extract of adrenal cortex on experimental neurosis in sheep. *Arch. Neurol. and Psychiat.*, Vol. 34, p. 973, 1935.
- Lockwood, J. E., and F. A. Hartman. Relation of the adrenal cortex to vitamins A, B and C. *Endocrin.*, Vol. 17, p. 501, 1933.
- Lockwood, J. E., D. R. Swan and F. A. Hartman. A further study of the relation of the adrenal cortex to vitamin C. *Am. J. Physiol.*, Vol. 117, p. 553, 1936.
- Long, C. N. H. The interrelationships of the glands of internal secretion concerned with metabolism. *Am. J. Med. Sci.*, Vol. 191, p. 754, 1936.
- Looney, J. M., and M. C. Darnell. The blood pressure—raising principle of adrenal cortex extracts. *J. Biol. Chem.*, Vol. 114, 1936.
- MacKay, E. M., and L. L. MacKay. Compensatory hypertrophy of the adrenal. *J. Exper. Med.*, Vol. 43, p. 395, 1926.
- McCance, R. A. Experimental sodium chloride deficiency in man. *Proc. Roy. Soc. London, Series B.*, Vol. 119, p. 245, 1936.
- Oliver, G., and E. A. Schaefer. The physiological effects of extracts of the suprarenal capsules. *J. Physiol.*, Vol. 16, p. 1, 1894.
- Reichstein, T. "Andrenosteron." *Über die Bestandteile der Nebennierenrinde II.* *Helvetica Chimica Acta*, Vol. 19, p. 223, 1936.

- Reiss, M., J. Balint and V. Aronson.** Compensatory hypertrophy of adrenals and the standardization of the adrenal cortex hormone on rats. *Endokrinol.*, Vol. 18, p. 26, 1936.
- Riddle, O., H. E. Honeywell and W. S. Fisher.** Suprarenal enlargement under heavy dosage with insulin. *Am. J. Physiol.*, Vol. 68, p. 461, 1924.
- Rogoff, J. M., and G. N. Stewart.** The influence of adrenal extracts on the survival period of adrenalectomized dogs. *Science*, Vol. 66, p. 327, 1927.
- Sataké, Y., M. Watanabé, and T. Sugawara.** Effect of fastening and of sensory stimulation upon the rate of epinephrine output from the suprarenal gland in dogs. *The Tohoku Jour. of Exp. Med.*, Vol. 9, p. 1, 1927.
- Sherman, H. C., and S. L. Smith.** *The Vitamins*. 2nd edition, p. 26, Chemical Catalogue Co., N. Y.
- Smith, P. E.** Hypophysectomy and replacement therapy. *Am. J. Anat.*, Vol. 45, p. 205, 1930.
- Stolz, F.** Synthese der wirksamen Substanz der Nebennieren. *Chem. Ztg.*, Vol. 30, p. 981, 1906.
- Swingle, W. W., and J. J. Piffner.** An aqueous extract of the suprarenal cortex which maintains the life of bilaterally adrenalectomized cats. *Science*, Vol. 71, p. 321, 1930.
- Takamine, J.** The isolation of the active principle of the suprarenal gland. *J. Physiol.*, Vol. 27, p. 29, 1901-02.
- Wheeler, T. D., and S. Vincent.** The question as to the relative importance to life of cortex and medulla of the adrenal bodies. *Trans. Roy. Soc. Canada*, Vol. 11, p. 125, 1917.
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